CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-449

ADMINISTRATIVE DOCUMENTS

Patent Information

1.	Active Ingredient	adefovir dipivoxil
2.	Strength	10 mg
3.	Trade Name	[redacted]
4.	Dosage Form & Route of Administration	tablet for oral administration
5.	Applicant Name	Gilead Sciences, Inc.
6.	NDA Number	21-449 (filed under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act)
7.	First Approval Date	Not yet approved*
8.	Exclusivity	Pursuant to 21 CFR 314.108(b)(2), no person may submit a 505(b)(2) application or ANDA for at least **5** years from the date of approval of this New Drug Application
9.	Patent Information	The following patents are listed in this NDA: • US Patent No. 4,808,716 • US Patent No. 4,724,233 • US Patent No. 5,663,159

* Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial of financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

Patent Certification

Certification of the following patents are provided:

- U.S. Patent No. 4,808,716
- U.S. Patent No. 4,724,233
- U.S. Patent No. 5,663,159

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Pediatric Summary

Pediatric Submssions Pediatric Exclusivity Activity Pediatric Pages for Pediatric Rule

Links to: Division Reports Division Assignments by Document Division Assignments by Discipline

There are 3 Pediatric Submissions, 1 Documents with Pediatric Exclusivity Activity, there are no Completed Pediatric Pages for the 1998 Rule

Pediatric Exclusivity Activity					
Appl.	Generic Name	Sponsor	PPSR Date	WR Date	Exclusivity Extension Granted?
[redacted]	ADEFOVIR DIPIVOXIL	GILEAD	5/11/01	4/12/02	
There were 1 Listings.					
Return to Pediatric Summary Search					

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-449 Supplement Type (e.g. SE5): _____ Supplement Number:_____

Stamp Date: March 20, 2002 Action Date: September 21, 2002

HFD-530 Trade and generic names/dosage form: HEPSERA (adefovir dipivoxil)

Applicant: Gilead Sciences, Inc Therapeutic Class: 7030170

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) or histologically active disease

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

√ No: Please check all that apply: ____Partial Waiver √ Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population
Disease/condition does not exist in children
Too few children with disease to study
There are safety concerns
Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population
Disease/condition does not exist in children
Too few children with disease to study
There are safety concerns
Adult studies ready for approval
Formulation needed

Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ **kg**____ **mo.**____ **yr.** 2 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** 17 **Tanner Stage**____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population
Disease/condition does not exist in children
Too few children with disease to study
There are safety concerns
√ **Adult studies ready for approval**
√ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): 01/01/2008

studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ **kg**____ **mo.**____ **yr.** 2 **Tanner Stage**____
Max____ **kg**____ **mo.**____ **yr.** 17 **Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Health Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marsha Holloman
10/23/02 02:11:26 PM

This paper peds page was included in action pkg on 09/20/02 & DFSed on 10/23/02.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9-11-02

FROM: Debra Birnkrant, M.D.
Director, Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Division Director's Memorandum for NDA 21-449 for Adefovir dipivoxil 10 mg for the Treatment of Chronic Hepatitis B (CHB)

This memorandum is written in support of the approval of adefovir dipivoxil for the treatment of patients with chronic hepatitis B. This regulatory action is based on the favorable risk/benefit profile of the drug. The risk/benefit profile was determined by the treatment benefit seen in pivotal trials, 437, 438, an open-label trial of adefovir in pre- and post-transplant subjects (study 435), a trial in lamivudine resistant subjects with compensated liver disease (study 461) and safety data from those studies submitted in support of the NDA. The risk/benefit assessment will be described below.

BACKGROUND:

A NDA for adefovir dipivoxil was originally submitted in 1999 for the treatment of HIV in combination with other antiretroviral therapies. Higher doses of adefovir dipivoxil were studied for the HIV indication and nephrotoxicity, manifested by a Fanconi-like syndrome, was seen after approximately 20 weeks of therapy. The NDA for adefovir dipivoxil or HIV was brought to an advisory committee and the committee voted that the risk/benefit profile was not acceptable for HIV treatment; the Agency agreed with this recommendation and a not-approvable letter was issued to the applicant. Recognizing that adefovir dipivoxil at lower doses looked promising for the treatment of chronic hepatitis B, Gilead Sciences pursued drug development in this area. NDA 21-449 for adefovir dipivoxil for the treatment of chronic hepatitis B was submitted on March 21, 2002 and went to the AVAC on August 6, 2002. The AVAC unanimously recommended approval of adefovir dipivoxil 10 mg for the treatment of chronic hepatitis B.

TRIAL RESULTS: EFFICACY

NDA 21-449 contained two principal studies, 437 and 438, which examined the use of adefovir dipivoxil in e-antigen positive and e-antigen negative subjects, respectively. Study 437 compared adefovir dipivoxil at 10 mg and 30 mg to placebo for the first 48 weeks and was designed to examine 10 mg versus placebo in the second 48-week period. Study 438 examined adefovir dipivoxil 10 mg compared with placebo for 48 weeks. The 10 mg dose was chosen for this study because it became apparent that adefovir dipivoxil 30 mg caused more renal toxicity than 10 mg in Study 437. Both studies had similar inclusion criteria and required examination of liver histology at baseline and 48 weeks. The primary endpoint for both studies was improvement in liver histology at week 48 that was defined as $\geq$ 2 point reduction in the Knodell necroinflammatory score without worsening of fibrosis. Secondary endpoints included changes in serum HBV DNA, improvement in ALT and seroconversion in study 437.

In both principal trials, treatment with adefovir dipivoxil resulted in a statistically significant improvement in liver histology at week 48. A positive treatment effect on fibrosis was also seen. Secondary endpoints went in the same direction as the primary endpoint with more subjects achieving ALT normalization, HBV DNA reduction, loss of e antigen and seroconversion(study 437) in the adefovir dipivoxil treated patients compared to placebo.

Three other important points will be made related to studies 437 and 438. After the 48-week endpoint, additional benefit was seen in studies 437 and 438. With continued treatment to 72 weeks, mean reductions in HBV DNA observed at week 48 were maintained. Secondly, in the principal studies, serum HBV DNA returned to baseline within 4 to 8 weeks following cessation of adefovir therapy. Lastly, study 437 was designed with a second 48-week period where patients who received adefovir dipivoxil 10 mg were re-randomized to 10 mg vs. placebo in an attempt to assess the need for additional therapy after 48 weeks of adefovir dipivoxil. A misallocation of dosing occurred during the second phase of the study and the objectives of the second phase could not be met. This did not impact the results of the first 48 weeks of trial 437.

To assess the efficacy and safety of adefovir dipivoxil in a lamivudine-resistant population, Gilead Sciences conducted studies 435 and 461. Study 435 is an on-going, open-label phase 3 study conducted in a lamivudine-resistant population and examined adefovir dipivoxil in the pre- and post-transplant setting. The primary endpoint was the time-weighted average change in serum HBV DNA from baseline to week 24. Results from this study revealed significant antiviral activity with reductions in HBV DNA similar to studies in patients with compensated liver disease and similar changes in HBV DNA and ALT normalization as compared to the principal studies. Study 461 evaluated adefovir dipivoxil with or without lamivudine in a patient population with compensated liver disease and with the lamivudine-resistant YMDD mutation.

Treatment with adefovir dipivoxil 10 mg resulted in significant decreases in serum HBV DNA measured at week 16 when compared to lamivudine monotherapy; no effect was seen in patients receiving lamivudine monotherapy. Also, please see the reviews by the primary medical officer and biostatistician, Dr. Tan Nguyen and Dr. Rafia Bhore, respectively.

TRIAL RESULTS: SAFETY

The applicant chose to put forth the 10 mg dose of adefovir dipivoxil as the to-be-marketed dose because it provided a balance between safety and efficacy. Safety issues identified in the principal studies related to the nephrotoxicity of adefovir dipivoxil . The 10 mg dose in studies 437 and 438 revealed minimal toxicity. Greater nephrotoxicity was seen in study 435, but this represented a more advanced patient population with patients who were either status post a liver transplant or on a waiting list for transplantation. Specifically, in study 437, 4% of patients receiving adefovir dipivoxil 10 mg developed increases in creatinine of $\geq$ 0.3 mg/dL by week 48 compared to < 1% in the placebo group. In study 438, only 3% developed elevated creatinine levels on adefovir dipivoxil compared to 5% in the placebo group. By week 96, 9-10% of patients receiving adefovir dipivoxil 10 mg developed an increase in serum creatinine of $\geq$ 0.3 mg/dL in studies 437 and 438 by Kaplan-Meier estimates; this has to be interpreted with caution as there was not a placebo group available for comparison.

More cases of renal toxicity were seen in study 435 with 26-30% of patients developing creatinine elevations > 0.3 mg/dL by week 48. Interpretation of these results is complicated by the uncontrolled study design, more advanced disease stage, concomitant use of nephrotoxic anti-rejection medication, abnormal renal function at baseline and limited data beyond 48 weeks. Nonetheless, we are recommending that wording be included in a boxed warning because of the serious nature of this adverse event; wording in the label will also advise monitoring of renal parameters while patients are receiving adefovir dipivoxil

Hepatitis flares occurred in patients who stopped adefovir dipivoxil. In clinical trials of adefovir dipivoxil, hepatitis flares with transaminase elevations 10 times the upper limit of normal or greater occurred in up to 25% of patients after discontinuation of adefovir. Most of these events occurred within 12 weeks of drug discontinuation. In patients with compensated liver disease, the flares were not generally accompanied by hepatic decompensation. As reflected in draft labeling, although most events appear to have been self-limited or resolved with reinitiation of treatment, severe hepatitis exacerbations, including fatalities, have been reported. Therefore, close monitoring of patients after stopping treatment will be recommended in labeling and wording describing these flares will be included in a boxed warning.

With the following caveats, i.e. genotypic analysis of DNA sequences from clinical specimens may not detect all viral variants present at < 30 % of a mixture

of mutant and wild-type viruses and resistance may be slow to develop during treatment with adefovir dipivoxil for hepatitis B, it is possible that clinically significant adefovir dipivoxil resistant mutants may emerge during longer-term treatment beyond 48 weeks, although none was seen during the clinical trials. With regard to viral resistance related to HIV, no patients in study 460i, a study of adefovir dipivoxil in co-infected subjects, developed K65R or K70E mutations. However, because adefovir has activity against HIV, the label will contain wording to assess HIV status prior to initiating therapy with adefovir dipivoxil for hepatitis B. Also, please see review by Dr. Lalji Mishra, reviewing microbiologist.

There were few deaths in studies 437 and 438; none was attributed to adefovir dipivoxil. Ultimate causality could not be assessed in the deaths in study 435, but the contributory role of adefovir dipivoxil could also not be completely ruled out in patients who died who also developed nephrotoxicity.

RISK/BENEFIT ASSESMENT:

To date, there are two marketed treatments for chronic hepatitis B, interferon-alpha and lamivudine. Both treatments have limitations. Interferon-alpha has common side effects, it is effective in only one-third of cases and it is not appropriate in the following patient groups: immunosuppressed, renal failure or on dialysis, and decompensated liver disease. Lamivudine is limited by the development of resistance that occurs at a rate of approximately 20% per year. Consequently, there is a need for new therapies for chronic hepatitis B, a disease that is the most common cause of cirrhosis and hepatocellular carcinoma.

Adefovir dipivoxil a nucleotide analogue, has been studied in both e-antigen positive and negative subjects. In these patient groups, adefovir dipivoxil 10 mg has shown a statistically significant and clinically relevant improvement in liver histology as demonstrated by improvement in the necroinflammatory and fibrosis scores compared to placebo. Secondary endpoints such as reduction in HBV DNA and ALT normalization were also statistically significant. Comparable results were also seen in studies of lamivudine-resistant disease where there are currently no marketed products.

In sum, although the ultimate goal of hepatitis B therapy is to prevent cirrhosis and hepatocellular carcinoma, these trials would take decades and would not be feasible. The studies in this NDA examined the effect of adefovir dipivoxil on histologic, serologic, virologic and biochemical markers of disease activity, endpoints similar to those found in the NDA for lamivudinine for CHB. Relying on histologic results and other surrogate markers of disease activity in a broad range of subjects, as presented in this application for adefovir dipivoxil, and considering the side effect profile, namely the rate and type of nephrotoxicity seen in the clinical trials, I fully support the approval of adefovir dipivoxil for treatment of chronic hepatitis B based on the data in NDA 21-449.

PHASE 4 COMMITMENTS:

1. Obtain long-term (5-year) follow-up information on patients rolled over from the pivotal clinical trials including the folowing:
   - risk for development of HBV resistance to adefovir dipivoxil
   - risk of drug-related adverse effects, particularly nephrotoxicity
   - maintenance of virologic suppression
   - durability of HBeAg and HBsAg seroconversion

2. Complete study 526 and submit the results to determine whether modeled dosing adjustments in renally impaired patients with CHB are appropriate.

3. Conduct a study to evaluate the efficacy, safety, and pharmacokinetics of adefovir dipivoxil in ethnic groups (African Americans, Hispanic Americans, and Asian Americans) who were underrepresented in the pivotal trials. The pharmacokinetic data in these different ethnic groups is necessary to make conclusions regarding the effects of race on adefovir PK.

4. Continue to perform genotypic and phenotypic analyses of HBV from patients receiving long-term adefovir therapy. Provide data on the genotypes and phenotypes of HBV from adefovir-treated patients with viral DNA rebound. Provide data on the genotypes and phenotypes of HBV and HIV-1 from adefovir-treated HBV/HIV-1 coinfected patients.

5. Conduct and/or submit the results of a study to evaluate combination therapy versus monotherapy in treatment naïve CHB patients to determine whether there is any added benefit of combination therapy.

6. Evaluate the drug-drug interaction potential of adefovir for medications that may be coadministered in patients with coexisting disease (s). The adefovir-didanosine and adefovir-probenecid interaction should be evaluated in addition to the compounds the sponsor has proposed (cyclosporine, tacrolimus, pegylated interferon-α, and tenofovir disoproxil fumarate).

7. Conduct a study to evaluate the pharmacokinetics of adefovir in geriatric patients.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 09-10-02

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-449, Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection

1.0 Background

HEPSERA is the tradename for adefovir dipivoxil (ADV), a nucleotide analogue with antiviral activity against HBV and HIV. Adefovir is phosphorylated intracellularly and the resultant adefovir diphosphate inhibits HBV and HIV polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA. The applicant, Gilead Sciences Inc., has submitted NDA 21-449 in support of a 10-mg tablet and a proposed dose of 10-mg daily for the indication of treatment of chronic hepatitis B in adults with evidence of active viral replication, persistently elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, or evidence of histologically active liver disease.

ADV was previously evaluated at doses of 60 and 120 mg for the treatment of HIV-1 infection, and the applicant submitted NDA . The application was determined to be nonapprovable based on a high incidence of nephrotoxicity at all doses, and equivocal evidence of efficacy for the 60-mg dose, which was the proposed to-be-marketed dose.

There are two therapeutic agents approved for the treatment of chronic hepatitis B. The first is a drug product, lamivudine. Although lamivudine has a very good tolerability profile, and a degree of efficacy similar to ADV, its utility is limited by the emergence of resistance in up to 25% of patients at one year. Resistance continues to emerge with prolonged use of lamivudine. Generally, once resistant viral variants are present, patients experience a recrudescence of hepatitis with increasing viral loads, increased transaminase levels, and an increase in active liver disease as seen histopathologically. The second agent, interferon alfa-2B, is a biologic product that must be administered parenterally for 6 months, and

many patients experience significant tolerability problems often requiring treatment discontinuation. Therefore, the availability of another safe and effective product for this indication would be a boon to the 400 million patients worldwide who suffer from chronic hepatitis B and need more treatment options.

For more detailed discussions of the safety and efficacy data, please refer to Dr. Tan Nguyen's clinical review, and Dr. Rafia Bhore's statistical review.

2.0 Summary of Efficacy

The efficacy of ADV has been demonstrated in three pivotal clinical trials, GS-98-437, GS-98-438, and GS-98-435. Studies 437 and 438 were double-blind, randomized, placebo-controlled studies of adults with compensated liver disease, adequate renal function, detectable HBV DNA, and ALT levels that were mildly elevated but <10 X ULN. The trial designs differed slightly such that subjects in 437 were HBeAg+, and those in 438 were HBeAg-. Study 437 was a three-arm trial and subjects were randomized 1:1:1 to placebo, ADV 10-mg daily, or ADV 30-mg daily. Study 438 had only placebo and ADV 10-mg arms.

The primary efficacy analysis for both 437 and 438, based on the comparison of the histology from paired liver biopsies, was performed at week 48. The primary efficacy endpoint was defined as a reduction from baseline of 2 points or more in the Knodell necroinflammatory score, with no concurrent worsening of the Knodell fibrosis score. A slightly different endpoint was used for the lamivudine for HBV application, that of reduction from baseline of 2 points or more in the total Knodell Histology Score. The modification to the endpoint for the ADV pivotal trials was made because it was felt that if fibrosis worsened, then the patient was not deriving benefit from treatment since fibrosis is the precursor to cirrhosis. Secondary endpoints included change from baseline in HBV DNA, proportion of patients with normalization of ALT, and proportion of patients with HBeAg loss, HBeAg seroconversion, HBSAg loss, and HBSAg seroconversion.

There was a statistically significant benefit of adefovir treatment over placebo with respect to the primary endpoint. In study 437, 67% of ADV 30-mg patients met the protocol definition of histologic improvement, compared to 59% of ADV 10-mg patients and 28% of placebo patients. A similar magnitude of effect was noted in study 438, with histologic improvement noted in 69% of subjects in the ADV 10-mg arm and in 36% of patients in the placebo arm. Results of analyses of secondary endpoints in both trials supported the positive finding of treatment benefit of adefovir over placebo. A greater proportion of patients in the adefovir treated arms achieved normalization of ALT, suppression of HBV DNA <400 copies/ml, and loss or seroconversion of HBeAg. Less than 1% of patients in all arms experienced a loss or seroconversion of HBsAg.

Additional subgroup analyses were conducted based on stratification factors of prior interferon treatment, baseline histology score, gender, and race (Caucasian vs. Asian). These analyses did not consistently identify any differences in

treatment response for any of these subgroups. Notably however, there were very few non-Asians and non-Caucasians enrolled in the clinical trials, which severely limits the assessment of the race-related treatment effects.

Study 435 is an ongoing, uncontrolled, open-label trial designed to evaluate the safety and efficacy of adefovir 10 mg daily in patients who are either post-liver transplantation, or waitlisted to receive liver transplantation. The majority of these patients had received prior lamivudine therapy and had developed clinical evidence of lamivudine resistance. Patients were assigned to one of three cohorts based on adequate vs. inadequate renal, hepatic, and hematologic function at baseline, as well as whether they had been previously treated with ADV. The primary efficacy endpoint for this study was the time-weighted average change in serum $\log_{10}$ HBV DNA from baseline to week 24 ($DAVG_{24}$). Since patients in cohort 2 were rolled over from another ADV trial, they did not have much additional reduction in HBV DNA levels by week 24 (-0.6 $\log_{10}$ copies/ml). In contrast, the patients in cohorts 1 and 3 who were ADV naïve achieved a reduction of HBV DNA (-3.5 $\log_{10}$ and –3.7 $\log_{10}$ copies/ml, respectively) that was comparable to that observed in studies 437 and 438. Analyses of secondary endpoints revealed improvements in ALT levels, and in Childs Pugh Turcotte scores. These findings provide evidence that adefovir has activity against lamivudine resistant virus, and efficacy in patients with more advanced liver disease than that of the patients enrolled in studies 437 and 438.

An additional phase 2/3, randomized, active-controlled study provided supportive evidence for the antiviral activity of ADV in the setting of lamivudine resistance. Study 461 enrolled 59 patients with history of clinical lamivudine resistance and confirmed genotypic evidence of the lamivudine resistance associated YMDD mutation. Subjects were randomized 1:1:1 to continued lamivudine therapy, adefovir 10 mg daily in addition to continued lamivudine therapy, or adefovir 10 mg daily alone. Analysis of the primary efficacy endpoint, $DAVG_{16}$, revealed no change for patients in the lamivudine alone arm, vs. a median change of approximately –2.86 $\log_{10}$ copies/ml in both of the ADV arms. The clinical significance of this degree of virologic change at week 16 is not known. However, the magnitude of the virologic change is similar to that seen in studies 437 and 438 at the same time point, indicative of the virologic activity of ADV in the presence of the lamivudine associated YMDD resistance mutations.

Overall, the treatment effect of ADV 10 mg was consistently demonstrated across studies, and in different patients subgroups including HBeAg+ and HBeAg- disease, in subjects with either compensated or advanced liver disease, and in the setting of lamivudine resistance. The applicant has demonstrated significant evidence for the efficacy of 10 mg of ADV.

3.0 Summary of Clinical Virology

Please refer the Dr. Lalji Mishra's Microbiology review for additional details. In addition to the evaluation of the activity of ADV in the setting of lamivudine resistance, the applicant also conducted extensive resistance analyses as part of the pivotal trials. Although the analyses are somewhat limited by the state of the technology for HBV genotyping and phenotyping, no mutation that was consistently associated with either clinical virologic failure, or decreased phenotypic susceptibility was identified. There were approximately 30 patients combined from both studies 437 and 438 who experienced protocol defined virologic rebound (an unconfirmed $\geq$ 1 $\log_{10}$ increase from nadir by week 48). However, even in this group of patients, no mutation in conserved or polymorphic sites was consistently identified. In retrospect, this definition of virologic rebound may have been too conservative, as a significant amount of natural fluctuation in HBV DNA levels is often observed. The applicant has reportedly developed an improved method of HBV phenotyping, and plans to use this method in future resistance analyses, and intends to reanalyze some of the samples from the pivotal trials. It is likely that mutations that result in decreased susceptibility and clinical virologic failure will ultimately occur; however, the genetic barrier may be relatively higher than for lamivudine.

4.0 Summary of Safety

In general, ADV was well tolerated and the adverse event profile was not significantly different from placebo with two notable exceptions. First, nephrotoxicity was noted in a significant number of patients treated with ADV 30 mg in study 437, and thus the sponsor decided to pursue the 10 mg dose as the to-be-marketed dose based on a lower incidence of nephrotoxicity at that dose. The study subjects in 437 and 438 had normal renal function per the enrollment criteria at baseline, and only 4% had a confirmed increase in serum creatinine to $\geq$ 0.3 mg/dl from baseline by week 48, compared to 2% in the placebo arm. Although this is a relatively conservative definition of renal dysfunction, an increase of $\geq$ 0.3 mg/dl in serum creatinine may represent a loss of up to 35% for a patient with normal renal function at baseline. Additionally, the risk may be cumulative, and was calculated to be 10% by the Kaplan Meier estimate at week 96, albeit in the absence of a control arm after week 48.

Not surprisingly, the incidence of nephrotoxicity was greater in study 435. The majority of these patients had some degree of renal impairment at baseline. In addition, most of these patients were on concomitant nephrotoxic medications and had significant concurrent morbidities. By week 48, 26% of the post transplant patients and 30% of the pretransplant patients had developed a serum creatinine increase $\geq$ 0.3 mg/dl by Kaplan Meier analysis. Determining the contributory role of ADV in these patients is further complicated by the uncontrolled design of the trial.

The second safety concern identified in the ADV trials is hepatic flare after discontinuation of ADV treatment. Presently, the appropriate duration of anti-HBV therapy is not known. The pivotal trials were designed such that after the first [48] weeks of treatment, subjects were re-randomized either to placebo or 10 mg. Thus, there were many subjects who were switched from either ADV 10 or 30 mg to placebo during the second 48 weeks. Although interpretation of the data is confounded by a misallocation of both ADV and placebo that occurred during the 2nd 48 weeks of study, up to 25% of these patients experienced an increase in transaminase levels to $\geq$ 10 X ULN. The phenomenon of hepatic flare has been previously reported with discontinuation of lamivudine therapy.

Despite the nephrotoxicity and the hepatic flares, the applicant has demonstrated the safety of ADV 10-mg daily dose. Descriptions of nephrotoxicity and hepatic flare will be included in the boxed warning and text warning sections of the PI to alert providers to these adverse reactions.

5.0 Summary of Regulatory Issues

As ADV is only the second antiviral drug for the treatment of chronic hepatitis B, this application was presented to the Antiviral Drugs Advisory Committee on August 6, 2002. The committee was asked to comment whether the applicant had demonstrated the safety and efficacy of ADV, and whether the application should be approved. The committee members agreed that substantive evidence of safety and efficacy had been presented, and voted unanimously in favor of approval. One caveat was that safety and efficacy data was not presented for the use of ADV of HIV/HBV coinfected patients, and a warning to this effect has also been incorporated into the PI.

6.0 Recommendation

I concur with the findings and recommendations as presented in the medical officer's review by Dr. Tan Nguyen. At this time, the applicant has provided substantive evidence for the safety and efficacy of ADV 10 mg in the treatment of adult patients with chronic hepatitis B. Therefore, the application should be approved.

/S/

Katherine A. Laessig, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 21-449

Drug: HEPSERA® (adefovir dipivoxil) for the Treatment of Hepatitis B Virus

Date: September 18, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Tan T. Nguyen, MD PhD, Medical Officer

Concurrence: Katherine A. Laessig, MD, Medical Team Leader
Jeffrey S. Murray, MD, MPH, Deputy Director
Debra B. Birnkrant, MD, Division Director

Subject: FDA 2nd REVISED PATIENT PACKAGE INSERT (PPI)

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for HEPSERA® submitted March 21, 2002. Also, reference is made to the Gilead Proposed Revised PPI submission dated September 18, 2002. Finally, reference is made to a teleconference between participants of FDA and Gilead on September 18, 2002.

The following are minor revisions to sections of the Patient Labeling for HEPSERA® (adefovir dipivoxil) Tablets by the Division of Surveillance, Research, and Communication Support (DSRCS) review dated September 12, 2002. The revisions are recommended in response to a request from DAVDP for the purposes of (1) clarification of the seriousness of hepatitis symptoms that can occur upon drug discontinuation and (2) to include information in the Patient Labeling to reflect the addition of information on the pregnancy registry in the Product Information (PI). DSRCS also recommends that the section, "What is the most important information I should know about HEPSERA?" remain in the patient labeling as it addresses serious, life-threatening information that appears in the PI as a Black Box Warning and provides the patient with important risk information.

DSCRC recommends no further revisions of the Patient Labeling ~~and DAVDP~~ concurs.

For ease of understanding, revisions are indicated with bolded and underlined type. Other bolded language should remain as is.

Please note that there are two bolded, underlined, and italicized requests for further information for inclusion in the patient label.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Attachment: FDA Proposed PPI

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 21-449

Drug: HEPSERA® (adefovir dipivoxil) for the Treatment of Hepatitis B Virus

Date: September 18, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Tan T. Nguyen, MD, PhD - Medical Officer
Robert O. Kume, PhD, Pharmacokinetics Reviewer

Concurrence: Katherine A. Laessig, MD, Medical Team Leader
Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader

Subject: PROPOSED REVISED LABELING COMMENTS FDA Version 5.0

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for HEPSERA® (adefovir dipivoxil) submitted March 21, 2002. Also, reference is made to Gilead's draft revised proposed labeling dated September 16, 2002. Reference is also made to a teleconference between participants of both Gilead and FDA held Wednesday, September 18, 2002.

Please respond to the following clinical, microbiological and PK review comments and requests:

1. Page 1: In the heading for the package Insert, please present the information as follows:

[redacted]

2 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 21-449

Drug: HEPSERA® (adefovir dipivoxil) for the Treatment of Hepatitis B Virus

Date: September 16, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Tan T. Nguyen, MD, PhD - Medical Officer

Concurrence: Katherine A. Laessig, MD, Medical Team Leader

Subject: PROPOSED REVISED LABELING COMMENTS
FDA Version 4.0

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for HEPSERA® (adefovir dipivoxil) submitted March 21, 2002. Also, reference is made to SN-030 containing draft revised proposed labeling dated September 11, 2002

Please respond to the following clinical and microbiology review comments and requests:

1. We essentially agree with your proposed text changes in the boxed warning section with the following changes (bolded):

[redacted]

3 page(s) of revised draft labeling has been redacted from this portion of the review.

[redacted]

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: **21-449**

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **August 28, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Ko-yu Lo, PhD, Chemist**

Concurrence: **Stephen P. Miller, PhD, Chemistry Team Leader**
James G. Farrelly, PhD, Pharmacology Team Leader

Subject: **CHEMISTRY REQUEST FOR INFORMATION**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for HEPSERA® (ADV) submitted March 21, 2002.

In order to finish the Chemistry and Toxicology reviews, we need the following information:

1. Please provide impurity profiles or Certificate of Analysis for the following drug substance batches that were used in the toxicology studies.

Batch Number:	Toxicology Study:
808-GS-93	Six month rat
GS-840-01	Fourteen day rat
TX840-96-01	One year monkey

[redacted]

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Tenofovir DF for the treatment of HIV infection**

Date: **August 26, 2002**

To: **Rebecca Coleman, Pharm D, Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Linda L. Lewis, MD, Medical Officer**

Concurrence: **Katherine A. Laessig, MD, Medical Team Leader**

Subject: **CLINICAL REVIEW COMMENTS**

Please refer to your [redacted] for tenofovir DF (TNV) for the treatment of HIV infection dated March 18, 1997. Also, please refer to your NDA 21-356 for tenofovir DF (VIREAD) dated May 1, 2001 and to the NDA approval letter containing postmarketing commitments dated October 26, 2001.

Reference is also made to SN-334 dated January 31, 2002, entitled *"Protocol GS-01-928: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF Plus an Optimized Background Regimen (OBR) versus OBR Alone in HIV-1 Infected, Antiretroviral Treatment-Experienced Children."* Finally, reference is also made to SN-396 dated June 25, 2002, entitled *"Protocol GS-02-983: A Phase 1, Open-Label, Single-Center Study of the Pharmacokinetics of Tenofovir DF Oral Suspension Administered in Combination with other Antiretroviral Agents in HIV-1 Infected Children."*

After a thorough review, we have the following clinical comments and recommendations:

1. **Protocol GS-01-928:** Since the initial review of this study, additional pharmacokinetic data confirm the drug-drug interaction between TNV and didanosine (ddI) resulting in increased ddI exposure when the drugs are given in combination. Increased ddI

exposure could potentially lead to increased toxicity, especially an increased risk of pancreatitis. Until the Division, Gilead, and Bristol-Myers Squibb (the sponsor of ddI) agree on appropriate dosing recommendations for the use of TNV and ddI in combination, it is appropriate to protect children from potential increased toxicity. This could be done by prohibiting the use of ddI in Study GS-01-928, delaying enrollment into the study, or by some other mechanism. Please propose a method by which to decrease the risk of potential toxicity related to the TNV/ddI interaction in Study GS-01-928.

2. **Protocol GS-02-983:** It is unlikely that a single dose of TNV will predispose patients who are receiving ddI to additional toxicity, even in those who might experience an increased ddI exposure. However, the potential for drug-drug interaction should be addressed in the informed consent for this protocol since the clinical relevance is unknown.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND:	**21-449**
Drug:	**Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**
Date:	**August 19, 2002**
To:	**Martine Kraus, PhD, Associate Director, Regulatory Affairs**
Sponsor:	**Gilead Sciences, Inc**
From:	**Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**
Through:	**Ko-yu Lo, PhD, Chemist**
Concurrence:	**Stephen P. Miller, PhD, Chemistry Team Leader**
Subject:	**CHEMISTRY NDA REVIEW COMMENTS AND REQUESTS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for HEPSERA® (ADV) submitted March 21, 2002.

With regard to adefovir dipivoxil drug substance:

1. Specification for [redacted]

DAVDP/HFD-530 • 5600 Fishers Lane • Rockville, MD 20857 • (301) 827-2335 • Fax: (301) 827-2471

2. Batch analysis data for drug substance (Table 4.1.7-3)

   Please perform statistical analysis (mean ± 3σ, range) on assay, impurities (individual and total, including [redacted] with production scale lots (i.e., Table 4.1.7-2, Lots 2166A to 7P-2166-AC-2P, AD403-2ctn1 to -AD403-14, including those manufacture after October, 1999). Please provide batch analysis table (*e.g.* Table 4.1.7-3) and tables of assay and impurity levels on stability.

3. Specification for drug substance

   We recommend that the DS specification be based upon production scale material and would like to discuss the acceptance criteria with you as soon as the updated batch analysis data is available for review.

With regard to the 10 mg tablet:

4. Stability of bulk powder blend [redacted] vs. stability of bulk tablets (Vol. 5, p.74, and Table 15 and Table 16)

   You stated that no significant change in strength and degradation product content of the powder blend was observed after three months of storage under ambient and refrigerated [redacted] but approximately [redacted] loss in label strength and [redacted] increase in degradation products was observed for the bulk tablets after three months storage at room temperature. Please explain the difference in stability. You stated that bulk tablets should be refrigerated prior to packaging. Has a hold time for the bulk tablets been established?

5. Please perform statistical analysis (mean ± 3σ, range) on potency, and impurity/degradent (individual and total) at release with lots reported in Table 4.2.6-2 and post submission lots if available. Please use a value of 0.01% for those impurity levels reported as none detected and a value of 0.05% for those reported as trace.

6. Please perform regression analysis on individual impurity/degradent data submitted on 5/02 and provide graphical display of the data set. We would like to discuss the acceptance criteria with you as soon as the updated statistical analysis is available for review.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: **21-449**

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **July 30, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Lalji Mishra, PhD, Microbiologist**

Concurrence: **Julian J. O'Rear, PhD, Microbiology Team Leader**
Katherine A. Laessig, MD, Medical Team Leader

Subject: **MICROBIOLOGY REVIEW COMMENTS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for TRADEMAME® (ADV) submitted March 21, 2002.

The following microbiology review comments and recommendations will be discussed at our teleconference on Tuesday, July 30 from 3:30 - 4:30 PM EDT (12-30 - 1:30 PM PDT):

1. The development of resistance to adefovir appears to be more complicated than that of lamivudine (3TC) and may require improved detection methods to characterize. Please discuss the limitations of the current surveillance procedures and propose improvements to them.

2. Please consider discussing with the advisory committee your plans for monitoring the emergence of adefovir-resistant HBV in chronically infected patients receiving long-term adefovir therapy, and adefovir-resistant HBV and HIV-1 in co-infected patients.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: **21-449**

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **July 29, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Robert O. Kumi, PhD, Pharmacokinetics Reviewer**

Concurrence: **Arzu Selen, PhD, Pharmacokinetics Team Leader (Acting)**
Katherine A. Laessig, MD, Medical Team Leader

Subject: **PHARMACOKINETIC (PK) REVIEW COMMENTS**

Please refer to your ——— for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for TRADEMAME® (ADV) submitted March 21, 2002.

The following PK review comments and recommendations will be discussed at our teleconference on Tuesday, July 30 from 3:30 - 4:30 PM EDT (12-30 - 1:30 PM PDT):

1. Please include a measure of variability for all grouped pharmacokinetic data in your study reports. For example, in addition to reporting geometric mean and its confidence interval, please provide arithmetic mean, standard deviation, and coefficient of variation values for adefovir pharmacokinetic parameters.

2. The following information was extracted from the summary table for ADV PK parameters in subjects with varying degrees of renal function. Please provide your rationale for including the subjects with bolded values in their respective groups.

Adefovir Pharmacokinetic Parameters in Subjects with Varying Degrees of Renal Function

	Renal Function			
	Normal (N = 7)	Mild Impairment (N = 8)	Moderate Impairment (N = 7)	Severe Impairment (N = 10)
Typical CL_{Cr} range	> 80 mL/min	50 – 80 mL/min	30 – 49 mL/min	< 30 mL/min
Range				

3. Please provide data that support your dosing recommendation for subjects with creatinine clearance less than 10 mL/min. In the absence of supporting data, the basis for your dosing recommendation is unclear.

4. Please provide data that evaluate the effect of long-term treatment on adefovir pharmacokinetics. At the 60-mg once daily dose, the apparent oral clearance of adefovir decreased (Week 52 vs. Week 2) with time, and was associated with nephrotoxicity. Although nephrotoxicity has not been observed with the 10-mg dose, it is advisable to confirm that adefovir PK do not change with time.

5. Please provide a summary in table form of the following data collected in the hepatic and renal impairment pharmacokinetic studies (Studies 474 and 478) for each individual:
   - patient id, gender, age, dose;
   - adefovir apparent clearance, creatinine clearance; and
   - the value/measurement of each component of the Child Pugh scores (such as, encephalopathy grade, ascites, serum albumin, bilirubin, and prothrombin time) and the total Child Pugh scores.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: **21-449**

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Chronic Hepatitis B**

Date: **May 29, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**

Concurrence: **Katherine A. Laessig, MD, Medical Team Leader**
Jeffrey S. Murray, MD, MPH, Deputy Director

Subject: **NOTIFICATION THAT THE PROPOSED TRADENAME ——— IS NOT ACCEPTABLE**

Please refer to your ——— for adefovir dipivoxil (ADV) for the treatment of chronic hepatitis B submitted on December 19, 1996. Reference is also made to your NDA 21-449 submitted March 21, 2002.

We have consulted with the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, Food and Drug Administration, regarding the acceptability of the tradename ——— for adefovir dipivoxil for the above indication. The response from DMETS is provided in the attachment below.

We concur with the findings by DMETS. Therefore, we recommend that another proposed trade name (or more than one, if possible) be substituted for ———. Please submit both paper (MS Word document) and electronic submissions (both MS Word and PDF documents) of the package insert, the patient package insert, and the carton and bottle labeling with the new proposed tradename(s) as soon as possible for review by the Division of Antiviral Drug Products and DMETS (DMETS is aware of the priority review status of this drug).

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **May 15, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Robert O. Kumi, PhD, Pharmacokinetics Reviewer**

Concurrence: **Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader**
Katherine A. Laessig, MD, Medical Team Leader

Subject: **CLINICAL PHARMACOLOGY (PK) REVIEW COMMENTS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-273 dated February 5, 2002 and entitled *"Plan for Analysis of Interaction between Adefovir, Cyclosporine, and Tacrolimus in Clinical Study GS-98-435."*

Your statistical analysis plan to evaluate the potential drug-drug interaction between adefovir and cyclosporine or adefovir and tacrolimus appears adequate. However, you should submit a formal protocol amendment to the ongoing clinical study protocol (GS-98-435) and address the following two comments:

1. Please adopt standard procedures for determination of the blood concentrations of both cyclosporine and tacrolimus.

2. Please indicate how many subjects you anticipate will participate in this drug-monitoring substudy. Because the pharmacokinetics of cyclosporine and tacrolimus are highly variable, a reasonable number of subjects should be included in appropriate cohorts to minimize the effect of variability on data interpretation.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: **21-449**

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **May 10, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Ko-yu Lo, PhD, Chemist**
Robert O. Kumi, PhD, Pharmacokinetics Reviewer

Concurrence: **Stephen P. Miller, PhD, Chemistry Team Leader**
Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader
Katherine A. Laessig, MD, Medical Team Leader

Subject: **CHEMISTRY AND BIOPHARMACEUTICAL REVIEW COMMENTS**

Please refer to your ——— for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to your NDA 21-449 for ——— (ADV) submitted March 21, 2002.

Please provide the information listed below:

1. Your rationale for selection of the dissolution method for ADV 10mg tablets. The information should include dissolution data in different media under different conditions (*e.g.,* paddle speeds.)

2. Two additional copies of the Method Validation Package (Vol. 1.007) for FDA Laboratories' use, as soon as possible.

3. Stability update by mid-August 2002. The information should include 12-month stability data on ——— lots D010C1, D011C2, and D012C2 and a reassessment of the proposed expiration-dating period with the updated long-term stability data.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **April 30, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**
Robert O. Kumi, PhD, Pharmacokinetics Reviewer

Concurrence: **Katherine A. Laessig, MD, Medical Team Leader**
Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader

Subject: **CLINICAL AND CLINICAL PHARMACOLOGY (PK) REVIEW COMMENTS SN-281**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-281 dated March 8, 2002, containing the final study report for Protocol GS-00-437 entitled "*A Phase 1, Open-label Parallel-Group Study to Evaluate the Pharmacokinetics (PK) of Adefovir Dipivoxil in Subjects with Normal and Impaired Renal Function.*"

After a thorough review, we have the following comments about the renal impairment study and adefovir dipivoxil dosing recommendations for patients with impaired renal function:

CLINICAL:

1. Please explain how you plan to monitor patients with renal insufficiency (particularly those who have moderate or severe disease) who may experience prolonged and high adefovir exposure for drug-associated adverse events.

2. Please explain how these adverse events will be managed and what parameter(s) you would use to decide whether adefovir treatment will be withheld or permanently discontinued in these patients.

CLINICAL PHARMACOLOGY (PK):

General Recommendation - The renal function of patients on adefovir should be monitored routinely because the drug causes nephrotoxicity at doses ≥ 30 mg once daily. In some patients with impaired renal function, adefovir exposure following administration of 10 mg may approach that observed in patients with normal renal function following administration of 30 mg.

Based on the pharmacokinetic information provided, we agree with your proposed dosing recommendations for patients with mild, moderate, and severe renal impairment. However, we do not think you have provided sufficient information to support the dosing recommendations for subjects with creatinine clearance < 10 mL/min and end stage renal disease (ESRD.) Subjects in these two groups will have adefovir exposure that greatly exceeds (> 5-fold increase in AUC) the exposure in patients with normal renal function. It is not clear how these exposures will affect the function of other tissues or body systems. Please address the following comments related to the renal impairment study.

1. In light of the high adefovir exposure that will be achieved in patients with CL_{Cr} < 10 mL/min or ESRD who receive adefovir dipivoxil once weekly, please provide a justification for the dosing recommendations in these patients.

2. Please provide your rationale for making the following statement regarding dosing in patients with CL_{Cr} < 10 mL/min: "[D]osage interval adjustment may be necessary on an individual basis to provide durable antiviral suppression on all days during the dosing interval." In your explanation, please indicate if these subjects will have a target adefovir exposure. It appears that subjects with severely impaired renal function (CL_{Cr} < 10 mL/min) will readily achieve therapeutic adefovir exposure (AUC.)

3. Please provide an update on the development of alternative adefovir dipivoxil formulations that may facilitate dosing in subjects with impaired renal function.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil (ADV) for the Treatment of Hepatitis B Virus**

Date: **April 2, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**

Concurrence: **Katherine A. Laessig, MD, Team Leader (Acting)**

Subject: **ADDITIONAL MO CLINICAL REVIEW COMMENTS SN-270**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-270 dated January 31, 2002, containing a new clinical study entitled *"Protocol GS-01-550: A Phase 3b, Open-label Program of Adefovir Dipivoxil in the Treatment of Patients with Lamivudine-Resistant Chronic Hepatitis B Infection Who Have Limited Treatment Options."*

After a thorough review, we find that it is safe to proceed with this Expanded Access Protocol (EAP.) However, we have the following comments for your consideration:

1. We are currently reviewing the submitted information on dosing of ADV in renally-impaired patients. We will convey our comments on this issue when the review is completed. Since the long-term safety profile of ADV in renally-impaired patients has not been clearly defined, we recommend that you do one of the following:
   - Delay enrollment of these patients in this protocol until such information becomes available, OR
   - Include a plan to closely monitor renal function (*e.g.*, monthly serum and urinary tests for ADV-associated nephrotoxicities.) Should the latter be instituted, please provide us periodic, safety-data updates for review.

2. We recommend that the frequency of laboratory monitoring for evidence of ADV-associated nephrotoxicities be increased (*e.g.*, every four weeks instead of every eight weeks) after five to six months of treatment, particularly in patients at risk for or having

had underlying renal impairment (see comment above). This is the period when most of these toxicities historically begin to emerge. The frequency can subsequently be modified as clinically indicated. We also recommend that urinalysis be included in the monitoring tests.

3. Please clarify whether ADV dipivoxil treatment would be terminated in patients who develop HBeAg seroconversion.

4. Please clarify whether patients will continue lamivudine treatment in this study.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **March 15, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**

Concurrence: **Jeffrey S. Murray, MD, MPH, Deputy Director**

Subject: **MO CLINICAL REVIEW COMMENTS SN-245**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-245 dated October 15, 2001, containing changes to the clinical study entitled *"Protocol GS-00-481: A Phase- 3b, Long-Term, Observational Study of the Durability of Seroconversion In Patients with Chronic Hepatitis B Virus Infection Who have Seroconversion while Participating in a Previous Gilead-Sponsored Study Of Adefovir Dipivoxil."*

After a thorough review, we find that it is safe to proceed. However, we have the following comments for your consideration:

1. We note that the frequency of study visits (*i.e.*, every 6 months) is relatively sparse to establish a meaningful database and therapeutic intervention in the event of disease relapse. Therefore, we recommend that patients be monitored at closer intervals initially (*e.g.*, every 3 months during the first year), and the frequency of visits can be subsequently modified as clinically indicated.

2. We recommend that a plan for monitoring drug resistance be incorporated in this study.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **March 7, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Kimberly A. Struble, Pharm D, Medical Team Leader (Acting)**

Concurrence: **Jeffrey S. Murray, MD, MPH, Deputy Director**

Subject: **MO CLINICAL REVIEW COMMENTS SN-270**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-270 dated January 31, 2002, containing a new clinical study entitled *"Protocol GS-01-550: A Phase 3b, Open-label Program of Adefovir Dipivoxil in the Treatment of Patients with Lamivudine-Resistant Chronic Hepatitis B Infection Who Have Limited Treatment Options."*

After a thorough review, we find that it is safe to proceed with this Expanded Access Protocol (EAP.) However, we have the following comments for your consideration:

1. Please amend protocol section 7.3.2. *"Events or Outcomes Not Qualifying as Serious Adverse Events"* to include the following:

   Please report the following events as severe adverse events (SAEs) if they (1) result in death; (2) result in a life-threatening situation; (3) cause inpatient hospitalization or prolongation of existing hospitalization; or (4) cause persistent or significant disability and/or incapacity.

   - Increase in Child-Pugh score
   - Spontaneous bacterial peritonitis
   - Ascites

- Encephalopathy
- Bleeding gastric and/or esophageal varices
- Hepatocellular carcinoma

2. We agree with your proposal to retain the physician investigator information (CVs and 1572s) on file and make the information available upon request rather than submitting it to the Division.

3. We also agree with your proposal to submit MedWatch reports to physician investigators in batches at an interval of every two weeks rather than at the time of submission to the Division.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **February 8, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**

Concurrence: **Kimberly A. Struble, Pharm D, Medical Team Leader (Acting)**

Subject: **MO CLINICAL REVIEW COMMENTS SN-264**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Additionally, reference is made to SN-264 dated January 17, 2002, containing materials for the teleconference (TCON) on Tuesday, January 22, 2002. Also, please refer to the minutes of the January 22nd TCON.

In addition to the proposed new drug application (NDA) content summarized in SN-264, we recommend that the NDA also contain the following items for studies GS-98-437 and GS-98-438:

1. Although you do not intend to submit data on the 30mg treatment group of study GS-98-437, we would like to have the data submitted for our review. Additionally, please include data on this treatment group in all safety analyses.

2. Data on disposition of patients, including the 30mg treatment group of study GS-98-437, should be presented as an organization chart similar to those recommended in Annex IV (a) and (b) of the International Conference on Harmonization (ICH) guideline entitled *"Structure and Content of Clinical Study Reports"* available on the FDA website at <http://www.fda.gov/cder/guidance/iche3.pdf>. The number of patients in each category should be clearly stated.

3. Please provide listings of patients who interrupted therapy and those who discontinued therapy, as shown in Annex V (page 38) of the ICH guideline listed above.

4. For each treatment group, including the 30mg treatment group of study GS-98-437, please provide a tabulated summary of numbers and percentages of patients who experienced grades 1, 2, 3, or 4 clinical adverse events for each body system.

5. For each treatment group, including the 30mg treatment group of study GS-98-437, please provide listings of patients with abnormal post-baseline serum creatinine, phosphorus, bicarbonate, urine glucose, and urine protein (where relevant) showing patient identification number, sex, age, race, baseline level, maximum (or minimum) post-baseline level, and toxicity grade, time of event occurrence, and disposition status.

6. For each treatment group, including the 30mg treatment group of study GS-98-437, please provide Kaplan-Meier plot of time to resolution of abnormal post-baseline serum creatinine ($\geq$ 0.5 mg/dL), phosphorus (toxicity grade 2 or higher), bicarbonate (toxicity grade 2 or higher), urine glucose (2+ or higher), and urine protein (2+ or higher), where relevant.

7. Please provide listings of patients and observations excluded from efficacy analysis as in Annex VI (page 39) of the ICH guideline listed above.

8. Please provide a comparative analysis on the demographics of study patient population versus patient population in the United States.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **January 22, 2002**

To: **Martine Kraus, PhD, Vice President, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Greg Soon, PhD, Biometrics Team Leader**

Concurrence: **Jeffrey S. Murray, MD, MPH, Deputy Division Director**

Subject: **STATISTICAL COMMENTS AND RECOMMENDATIONS - ELECTRONIC NDA SUBMISSION OF DATASETS AND PROGRAMS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Also, please refer to SN-264 dated January 17, 2002 entitled *"General Correspondence: Gilead Sciences-FDA Teleconference of January 22, 2002 11:00 AM EDT (8:00 AM PDT."* Reference is also made to the End of Phase 2 Meeting with the Division on August 10, 2001and to the teleconference (TCON) between Gilead Sciences and FDA on January 22, 2002.

Finally, reference is made to two guidance documents found on the FDA website: *"FDA Guidance Document for Industry: Providing Regulatory Submissions in Electronic Format — General Considerations"* <http://www.fda.gov/cder/guidance/2867fnl.pdf> and *"FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs"* <http://www.fda.gov/cder/guidance/2353fnl.pdf>.

Following the TCON, we discussed the electronic NDA submission of datasets and programs with Randy Levin, MD, Division of New Drug Products, Office of New Drugs, Center for Drug Evaluation and Research. Based on these conversations, we renew our request for the datasets and programs discussed during yesterday's TCON.

1. Please send the SAS program files as ASCII files (*.sas) included with the SAS transport files.

2. The SAS programs must be compatible with SAS 6.12 so we can reproduce their results.

3. Please send these files to: Central Document Room
   Center for Drug Evaluation and Research
   Food and Drug Administration
   12229 Wilkins Avenue
   Rockville, MD 20852

4. Should you still have any questions, please contact Dr. Levin at 301-594-5411 for further information.

1. Electronic datasets (raw, intermediate/derived, final analysis), programs, and algorithms (if any);

2. Formats of all variables (*e.g.,* SAS format catalogs) and macros used;

3. A flowchart explaining how the datasets were derived and which programs were used to create the derived and final analysis datasets;

4. A list of the names of programs/datasets used to create tables within the text of the Phase III Clinical Study Reports;

5. Electronic MS Word documents of the main Clinical Study Reports, Protocols of Phase III studies, and Statistical Data Analysis Plans for these studies;

6. In the final submission please provide detailed explanations for those patients for whom biopsies were missing or unavailable (see Page 53 of [redacted] SN-228).

7. Currently, the estimates for treatment effects are based on relative risk. Since the primary analysis for biopsy is the Cochran-Mantel-Haenszel (CMH) test, please provide estimates based on differences in proportions, which are consistent with the CMH test used (see Page 53 [redacted]/SN-228; also discussion with Gilead counterpart during the meeting of August 10, 2001.)

8. Please submit all available unblinded data from Protocol 437 with the NDA submission.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **January 18, 2002**

To: **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer**

Concurrence: **Jeffrey S. Murray, MD, MPH, Deputy Division Director**

Subject: **MO COMMENTS ON Pre-NDA ISSUES**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Also, please refer to electronic mail messages between Martine Krause and Marsha Holloman for the period beginning September 27, 2001 and ending December 11, 2001.

For clarity and ease of understanding, the pre-NDA questions are in **BOLD CAPITAL LETTERS** and the pre-NDA answers are in regular 12-point text.

1. CONTENT AND FORMAT OF THE NDA SAFETY UPDATE

At your request, we will postpone this discussion for now. However, if you are prepared to submit a proposal, we can discuss it at the requested teleconference.

2. FINANCIAL DISCLOSURE

We will let you know whether you need to submit financial disclosure information for clinical investigators for this open-label study under 21CFR54.2 during the teleconference scheduled for Tuesday, January 22, 2002.

3. CASE REPORT FORMS (CRF)

We agree with your proposal to submit in Section 12 only the CRFs for patients who died or discontinued study drug due to an adverse event. However, please be advised that we may, in the course of the review, request CRF on patients who experienced serious adverse events, if necessary.

4. PROTOCOL GS-94-404

We agree that for this study, you will provide TFLs but no datasets or documentation in the NDA submission.

5. LOCATION OF PATIENT LISTINGS IN THE NDA SUBMISSION

We strongly recommend that patient listings be included in the clinical study reports.

Additionally, we request that you provide analyses similar to those requested by your Data Monitoring Committee in the letter dated November 9, 2000, in the NDA submission.

Specifically, we are want analyses on the following:

(1) dropouts (see issue # 2 of the letter);

(2) laboratory data (see issue # 5 of the letter);

(3) nephrotoxicity (see issues # 6, 7 and 8 of the letter); and

(4) transaminase "flares" (see issues # 10, 11 of the letter.)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND:	[redacted]
Drug:	**Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**
Date:	**January 10, 2002**
To:	**Martine Kraus, PhD, Associate Director, Regulatory Affairs**
Sponsor:	**Gilead Sciences, Inc**
From:	**Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**
Through:	**Tan T. Nguyen, MD, PhD, Medical Officer**
Concurrence:	**Jeffrey S. Murray, MD, MPH, Deputy Division Director**
Subject:	**MO CLINICAL REVIEW COMMENTS PROTOCOLS GS-00-480 and GS-00-481**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Also, please refer to SN-245 dated October 28, 2001, entitled *"Protocol Amendments: Change in Study Protocol GS-98-438 and New Study Protocols GS-00-480 and GS-00-481."*

Protocol GS-00-480: *"An Open-Label, Continued Access Study of Adefovir Dipivoxil for Patients with Chronic HBV Infection Who Have Completed a Gilead-Sponsored Study of Adefovir Dipivoxil"*

The protocol is safe to proceed. However, we request that you provide responses to the following comments:

1. Please clarify whether patients without evidence of virologic and/or histologic responses would be enrolled in this study. If so, please explain the rationale for additional ADV therapy in these patients.

2. We recommend that you monitor serum HBV DNA levels periodically and provide the results to the patients and the investigators so that informed decisions can be made about whether ADV treatment should be continued indefinitely.

Protocol GS-00-481: *"A Phase 3-b, Long-Term, Observational Study of the Durability of Seroconversion in Patients with Chronic Hepatitis B Virus Infection Who Have Seroconverted While Participating in a Previous Gilead-Sponsored Study of Adefovir Dipivoxil"*

The protocol is safe to proceed. However, we request that you provide responses to the following comments:

3. We note that the frequency of study visits is every 6 months. We recommend that patients be monitored at closer intervals initially (*e.g.*, every 3 months during the first year) and the frequency of visits can be subsequently modified as clinically indicated. This will establish a meaningful database for therapeutic intervention in the event of disease relapse.

4. We recommend that a plan for monitoring drug resistance be incorporated into this study.

Protocol GS-98-438: *"A Phase III Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with Presumed Precore Mutant (HBeAg-/Anti-HBe+/HBV DNA+) Chronic Hepatitis B Virus Infection"*

We do not have any comments on this amended protocol.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir for the treatment of Hepatitis B Virus**

Date: **September 18, 2001**

To: **Rebecca Coleman, Pharm D, Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Lalji Mishra, PhD, Microbiologist**

Concur: **Frederic J. Marsik, PhD, Microbiology Team Leader**
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader, Acting Deputy Director

Subject: **Microbiology Review Comments**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-047, SN-061, and SN-223 containing information about the HBV DNA PCR assay in general and Roche Amplicor HBV Monitor™ Test in particular.

After a thorough review, we have the following microbiology comments:

1. You have adequately addressed our concern about the sensitivity of Roche Amplicor HBV Monitor™ Test.

2. Please provide additional data on the specificity of Roche Amplicor HBV Monitor™ Test.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus (HBV)**

Date: **August 27, 2001**

To: **Alan Taylor, PhD, Vice President, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Rafia Bhore, PhD, Mathematical Statistician**

Concurrence: **Greg Soon, PhD, Biometrics Team Leader**
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: **STATISTICAL COMMENTS AND RECOMMENDATIONS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection in adults submitted December 19, 1996. Also, please refer to SN-226 dated July 23, 2001 entitled *"General Correspondence: Request for Concurrence on Plans for Providing Electronic Datasets to the NDA for ADV/HBV."* Reference is also made to the End of Phase 2 Meeting with the Division on August 10, 2001.

After a thorough review of your proposals for the format of electronic datasets to the NDA for ADV submitted to your [redacted] /SN 226 and dated July 23, 2001, we find that all are acceptable.

In addition, please provide the following materials and information:

1. Electronic datasets (raw, intermediate/derived, final analysis), programs, and algorithms (if any);

2. Formats of all variables (*e.g.*, SAS format catalogs) and macros used;

3. A flowchart explaining how the datasets were derived and which programs were used to create the derived and final analysis datasets;

4. A list of the names of programs/datasets used to create tables within the text of the Phase III Clinical Study Reports;

5. Electronic MS Word documents of the main Clinical Study Reports, Protocols of Phase III studies, and Statistical Data Analysis Plans for these studies;

6. In the final submission please provide detailed explanations for those patients for whom biopsies were missing or unavailable (see Page 53 of /SN-228).

7. Currently, the estimates for treatment effects are based on relative risk. Since the primary analysis for biopsy is the Cochran-Mantel-Haenszel (CMH) test, please provide estimates based on differences in proportions, which are consistent with the CMH test used (see Page 53 /SN-228; also discussion with Gilead counterpart during the meeting of August 10, 2001.)

8. Please submit all available unblinded data from Protocol 437 with the NDA submission.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

Date: **May 23, 2001**

To: **Ellen F. Wallace, PhD, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Robert O. Kumi, PhD, Pharmacokinetics Reviewer**

Concur: **Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader**
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: **PHARMACOKINETICS (PK) REVIEWER COMMENTS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-189 dated April 16, 2001, containing your revised PK plan, your response to FDA's request for further information, and a statement describing the transfer of obligations from Gilead Sciences to contract research organizations for the new protocol. Finally, reference is made to a new protocol and consent form for study GS-00-474 entitled "*A Phase 1, Open-Label Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Adefovir Dipivoxil in Subjects with Normal and Impaired Hepatic Function.*"

We have the following comments and recommendations on SN-189:

1. Your revised PK program plan is acceptable. However, at some point, we want to discuss the need for the cyclosporine and tacrolimus drug-interaction study.

2. Please send us any information you have about the potential effect of ADV on p-glycoprotein and the potential for ADV to induce metabolic enzymes.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

Date: **April 13, 2001**

To: **Ellen F. Wallace, PhD, Manager, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Robert O. Kumi, PhD, Pharmacokinetics Reviewer**

Concur: **Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader**
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: **PHARMACOKINETICS REVIEWER COMMENTS**

Please refer to your [redacted] for Adefovir Dipivoxil (ADV) for the treatment of hepatitis B virus infection submitted December 19, 1996 and to [redacted] for ADV for the treatment of HIV infection. Reference is also made to manufacturing and controls information concerning the ADV 10mg tablet submitted to [redacted] SN-334 dated July 22, 1998, and incorporated into [redacted] by cross-reference. Also, please refer to SN-162 dated December 20, 2000, containing your request for waiver of bioequivalence study.

1. The data presented in this submission to support the changes in the 10mg ADV tablet satisfy the criteria for waiver of evidence of the *in vivo* bioequivalence. Therefore, your request for a waiver of bioequivalence is granted.

2. The new 10mg ADV tablet may be used in your proposed Protocol GS-00-476 entitled, "*A Phase 1, Randomized, Open-Label, Pharmacokinetic Study in Healthy Volunteers to Assess the Effect of Food on the Bioavailability and Pharmacokinetics of the Intended Commercial Formulation of Adefovir Dipivoxil 10 mg Tablets,*" submitted in January 2001.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 23, 2001

To: Alan S. Taylor, Ph.D.
Vice President, Drug Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Robert Kumi, Ph.D., Pharmacokinetics Reviewer, HFD-530
Kellie Reynolds, Pharm.D., Pharmacokinetics Team Leader, HFD-530

IND: —— (serial number 168)

Subject: Clinical Pharmacology and Biopharmaceutics Comments for Protocol GS-00-475

The following comments are being conveyed on behalf of Dr. Robert Kumi and are directed towards serial number 168.

1. Please calculate urinary excretion parameters for adefovir.

2. Please decrease the duration of Treatment A, as steady state will be reached within 3 days, or indicate why 7 days of treatment with adefovir dipivoxil are warranted.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 17, 2001

To: Alan S. Taylor, Ph.D.
Vice President, Drug Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Grace N. Carmouze, Regulatory Project Manager, HFD-530

Through: Greg Soon, Ph.D., Acting Statistical Team Leader, HFD-530
Jeffrey Murray, M.D., M.P.H., Medical Team Leader, HFD-530

IND: —— (serial numbers 158 and 161)

Subject: Statistical Comments to the unified analysis plan for GS-98-437 and GS-98-438

The following comments are being conveyed on behalf of Dr. Greg Soon and are directed towards serial numbers 158 and 161.

1. The difficulties of analysis are in the handling of subjects who refuse biopsies at the end of one year and losses to follow up. Based on the experience of Epivir® trials we expect missing biopsy rates to be below 20%.

2. Please consider that subjects who discontinued treatment due to various reasons (toxicity, response, or lack of response, etc.) should be followed and one-year biopsies should be pursued. These results can be incorporated into the final analysis.

3. Please note that the final decision on efficacy will be based on ranges of analyses to ensure the robustness of the conclusion with respect to the handling of the biopsies. For example, instead of treating all missing biopsies as failures, FDA will examine cases where a proportion of missing values is regarded as failures in both arms.

4. It is also recommended that for analyses using the primary endpoints that multiple imputation or other techniques to impute the outcomes for mission biopsies be considered. The predictors should include viral load and ALT measurements at baseline and end of one year, plus other appropriate predictors.

5. Please consider stratifying the analyses by the randomization stratification variables.

6. Please send your draft proposal via e-mail or facsimile transmission for comment.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

/S/

Grace N. Carmouze
Regulatory Project Manager
Division of Antiviral Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: —— 'SN-136

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

Date: **December 8, 2000**

To: **Alan S. Taylor, PhD, Vice President, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Robert O. Kumi, PhD, Pharmacokinetics Reviewer**

Concur: **Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader**
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: **PHARMACOKINETICS REVIEWER COMMENTS**

Please refer to your —— for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-136 containing the following two protocols:

1. Protocol GS-00-427 entitled "*A Randomized, Double-Blind, Placebo-Controlled Phase 1–2 Study of the Pharmacokinetics, Safety, and Antiviral Activity of Adefovir Dipivoxil in Nucleoside Treatment-Naïve HBV-Infected Patients,*" dated August 14, 2000.

2. Protocol GS-00-477 entitled "*An Open-Label Phase 1-2 Study of the Effect of Ethnicity on the Pharmacokinetics, Safety, and Antiviral Activity of Adefovir Dipivoxil 10 mg/day in Nucleoside Treatment-Naïve HBV-Infected Patients,*" dated August 14, 2000.

The protocols do not indicate where plasma samples collected at the different study centers will be assayed. If plasma samples are not assayed at a central location, please provide documentation of assay cross-validation in the final study reports.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND/NDA [redacted] SN-134

DRUG: Adefovir Dipivoxil to treat Hepatitis B infection

DATE: September 19, 2000

TO: Ellen Wallace, Manager, Regulatory Affairs

SPONSOR: Gilead Sciences, Inc

FROM: Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, HFD-530

THROUGH: Tan T. Nguyen, MD, PhD, Medical Officer

CONCUR: Jeffrey S. Murray, MD, MPH, Medical Review Team Leader

SUBJECT: CLINICAL COMMENTS AND REQUEST FOR INFORMATION

In vitro evidence shows that YMDD mutant HBV has decreased replication competence, and thus, is less "fit" than the wild type HBV. Results from a number of long-term clinical studies also indicate that patients with YMDD mutant HBV who remain on lamivudine therapy continue to clear HBeAg and maintain lower serum HBV DNA and ALT levels, relative to baseline values. More importantly, most of these patients continue to have histologic improvement. Consequently, it has been suggested in current literature that, despite the emergence of YMDD mutant HBV, most patients may continue to derive clinical benefit from lamivudine therapy. Therefore, if the emergence of YMDD mutant HBV is not associated with clinical worsening of the disease in most patients on lamivudine therapy, why is additional therapeutic intervention (*i.e.*, adefovir or adefovir plus lamivudine) necessary in these patients? Additionally, what is the long-term clinical benefit of additional therapeutic intervention in these patients, and how can DAVG16 be used as a valid "surrogate" marker for this?

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted] SN-110

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Infection

Date: May 24, 2000

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, HFD-530

Through: Greg Soon, PhD, Statistical Reviewer

Concur: Girish Aras, PhD, Statistical Review Team Leader
Jeffrey Murray, MD, MPH, Medical Officer Team Leader

Subject: Statistical Reviewer's Comments

Please refer to your IN [redacted] /SN-110 for adefovir dipivoxil for the treatment of patients with chronic hepatitis B virus infection and to Protocol GS-98-438, entitled *A Phase III, Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil of Patients with Presumed Pre-Core Mutant (HBeAg⁻/Anti-HBE+/HBV DNA+) Chronic Hepatitis B Virus Infection."*

Dr. Soon asked me to send the following comments to you:

1. Please refer to the previous clinical and statistical comments regarding the efficacy endpoints and analyses for study GS-98- 437. Please make the appropriate changes and submit them as a protocol amendment to [redacted].

2. Because your pivotal trials are very similar in both design and conduct, please develop a unified analysis plan that will ensure consistency across the pivotal studies and the other efficacy studies. This integrated analysis plan should provide details on how you propose to handle missing values, early discontinuations, dose reduction, and treatment switches. Also, please include detailed information about the performance of your analyses. Please submit your unified analysis plan for Agency review.

3. Please clarify the randomization procedure. Will the centralized randomization be actually an adaptive randomization? If yes, please propose appropriate analysis methods.

4. In the sample-size calculation, you assumed a missing rate of 30% and a treatment difference of 30%. Please be aware that if indeed the missing rate is close to 30%, the data will be difficult to interpret, because the results will be very sensitive to how the missing values are handled. Please attempt to minimize such missing values and take the sensitivity analysis into consideration when determining the sample size.

   Study GS-98-437 faces the same issue. Please note, however, the assumed treatment effects differ in the two studies. Please explain this difference. Additionally, please note that high missing rate in the first year will severely limit the interpretation of the results in the second year.

5. Please exclude subjects who do not take any study medication from the efficacy analyses.

6. Please closely follow and evaluate those subjects who have dose reductions or who have discontinued the study drug in the same manner as you do other study participants. In particular, please document any additional anti-HBV medication(s) taken by patients in this protocol.

   Please perform subgroup analyses for those subjects who discontinued study medication, subjects who have dose reductions, and subjects who complete the 12 months of randomized treatment.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted]/SN-101

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

Date: **February 25, 2000**

To: **Bridget P. Binko, Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, HFD-530**

Through: **Tan T. Nguyen, MD, PhD, Medical Officer Reviewer**

Concur: **Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader**

Subject: **MEDICAL REVIEWER COMMENTS**

Please refer to your [redacted]/SN-101, Protocol GS-98-437 entitled *"A Double-Blind Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with Chronic HBeAG + Hepatitis B Virus Infection."* The following are comments from the medical reviewer.

The protocol, as amended, does not raise any additional safety issues. However, it poses several design issues that should be addressed.

1. Please clarify whether there is a plan to resume dosing adefovir at the original dose in patients who have received adefovir dose reduction for nephrotoxicity.

2. According to the protocol, a substantial number of patients (17/34; 50%) treated with adefovir 30 mg daily in Study GS-96-412 have developed laboratory evidence of nephrotoxicity by week 44 of the extension phase requiring dose reduction or interruption. It is unclear to us whether any of these patients have been able to resume the initial adefovir dosing. Efficacy analyses may potentially be compromised if nephrotoxicity necessitates prolonged (or permanent) reduction or interruption of adefovir treatment in a similar proportion of patients in the current study. Please comment on how this issue will be addressed.

3. Please comment whether re-randomization of only group 2 patients at the beginning of year 2 will compromise the blinded nature of the study.

4. According to the protocol, patients who receive a reduced dose of adefovir at month 12 will continue to receive the reduced dose in the second year of the study. This would essentially create another treatment group, *i.e.*, adefovir 5 mg daily. It is noted that the adefovir 5 mg daily produced less anti-HBV activity than adefovir 30 mg daily in a previous dose-ranging study (Study GS-96-412). Please comment on why this less active dose would be offered.

5. The original protocol indicated, and we concurred, that creatinine clearance would be obtained at the end of year 1 and year 2 of the study. Please clarify whether this test is still included in this revised protocol.

6. Please explain what hematologic parameter(s) will be tested every three months with "banked" specimens as indicated in the Schedule of Assessments (Section 5.1).

7. Please indicate in the informed consent form that the study is also designed to evaluate the safety of L-carnitine.

8. We recommend that the sentence "Information from small number of patients taking this dose [10 mg daily adefovir] ... active in suppressing the hepatitis B virus" (Informed consent form, page 5)" be deleted unless substantial and systematically-collected data have been obtained to demonstrate the "significant" antiviral activity of this dose.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: [redacted] /SN-077

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: August 23 1999

To: Bridget P. Binko, Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, HFD-530

Through: Tan T. Nguyen, MD, PhD, Medical Officer Reviewer

Concur: Jeffrey Murray, MD, MPH, Medical Officer Team Leader

Subject: Medical Reviewer Comments

Please refer to your [redacted] /SN-077, Protocol GS-98-437 entitled *"A Double-Blind Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with Chronic HBeAG + Hepatitis B Virus Infection."* The following are comments from the medical reviewer:

1. If you plan to dose the adefovir 30-mg/day treatment group for 1 year, we recommend that these patients be appropriately followed for earliest evidence of nephrotoxicity for dose adjustment or discontinuation of study drug. In that case, please clarify if the 30-mg/day treatment group will again be included in the primary efficacy analysis.

2. The data included in Submission # 077 suggest that nephrotoxicity is stabilized with adefovir dose reduction. However, it is premature to conclude that nephrotoxicity is "reversible" based on the available data. For example, seven out of 11 patients with creatinine levels elevated to $\geq$ 0.3 mg/mL of baseline values did not have creatinine levels returning to < 0.3 mg/mL at the last visit (1.5 to 2 months later). It is of interest to follow these patients to determine whether nephrotoxicity would recur or worsen upon restarting at the full dose. Please update us periodically with follow-up data as they become available.

3. Please provide us with a copy of the study protocol once it is finalized for review.

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